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Characterization of Dyspnea in Veteran Lung Cancer Survivors Following Curative-Intent Therapy

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Purpose: Dyspnea is highly prevalent in lung cancer survivors following curative-intent therapy. We aimed to identify clinical predictors or determinants of dyspnea and characterize its relationship with functional exercise capacity (EC).

Methods: In an analysis of data from a cross-sectional study of lung cancer survivors at the VA San Diego Healthcare System who completed curative-intent therapy for stage I-IIIA disease ≥1 mo previously, we tested a thorough list of comorbidities, lung function, and lung cancer characteristics. We assessed dyspnea using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13 (LC13) and functional EC using the 6-minute walk. We replicated results with the University of California San Diego Shortness of Breath Questionnaire.

Results: In 75 participants at a median of 12 mo since treatment completion, the mean ± SD LC13-Dyspnea score was 35.3 ± 26.2; 60% had abnormally high dyspnea. In multivariable linear regression analyses, significant clinical predictors or determinants of dyspnea were (β [95% CI]) psychiatric illness (−20.8 [−32.4 to −9.09]), heart failure with reduced ejection fraction (−15.5 [−28.0 to −2.97]), and forced expiratory volume in the first second of expiration (−0.28 [−0.49 to −0.06]). Dyspnea was an independent predictor of functional EC (−1.54 [−2.43 to −0.64]). These results were similar with the University of California San Diego Shortness of Breath Questionnaire.

Conclusion: We identified clinical predictors or determinants of dyspnea that have pathophysiological bases. Dyspnea was independently associated with functional EC. These results have implications in efforts to reduce dyspnea and improve exercise behavior and functional EC in lung cancer survivors following curative-intent therapy.

Key Words: exercise • lung neoplasms • patient-reported outcome measures • survivorship • symptom assessment

Exercise has been shown to be effective in improving function and quality of life (QoL)[1] and is recommended by the American College of Sports Medicine[2] and the American Cancer Society[3] for many cancer survivors. However, the evidence of effectiveness is not as consistent in lung cancer survivors.[4] This inconsistency may be related to characteristics unique to lung compared with other cancer survivors, including differences in age, comorbidities, and the effects of lung cancer and its treatment on exercise capacity (EC). Many patients with lung cancer are elderly and have major comorbidities that include chronic obstructive pulmonary disease (COPD) and heart failure that may limit EC.[5] Also, curative-intent therapy of lung cancer necessitates the removal and/or destruction of lung tissue, which may further exacerbate symptoms and impede cardiopulmonary function and EC in some patients.

Symptom burden may limit exercise in lung cancer survivors. Following lung cancer resection surgery, dyspnea worsens[6] partly due to a loss of 10-15% of lung function.[7] Clinically significant dyspnea has been shown to be prevalent in >50% of lung cancer survivors.[8-11] As a result, lung cancer survivors may avoid exercise to prevent dyspnea. In time, this avoidance can lead to a downward spiral of health related to physical function, symptom burden, and QoL (see Supplemental Digital Content 1, available at: http://links.lww.com/JCRP/A132), all of which are important survivorship issues in lung cancer.[12] Therefore, the characterization of dyspnea in lung cancer survivors may provide important insights into factors associated with dyspnea and may facilitate interventions to improve exercise, function, and QoL in these patients.

The purpose of this project was to identify clinical predictors or determinants of dyspnea in lung cancer survivors following curative-intent therapy and analyze the relationship between dyspnea and functional EC. It is believed that optimization of underlying comorbidities including cardiopulmonary disease may be important in improving exercise, function, and QoL in these patients.

METHODS

In a previous cross-sectional study to assess functional EC and patient-reported outcomes in lung cancer survivors following curative-intent therapy, exploratory patient-reported outcomes assessments identified abnormally high dyspnea in ≈ 60% of participants[13] as assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13 (LC13).[14] In this study, additional participants were enrolled to identify clinical predictors or determinants of dyspnea and explore its relationship with functional EC. Guideline recommendations for Strengthening the Reporting of Observational studies in Epidemiology were used to report findings.[15] The VA San Diego Healthcare System (VASDHS) Institutional Review Board approved this protocol (#H150158).

At the VASDHS, all patients diagnosed with primary or progressive/recurrent lung cancer are presented to a weekly multidisciplinary chest tumor board for management

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planning. From a list of consecutive patients presented at the VASDHS chest tumor board, kept to ensure quality clinical care, potentially eligible patients were identified. Between August 2016 and April 2018, consecutive patients were recruited by informational letters mailed to those whose lung cancer was diagnosed and/or managed at the VASDHS since October 2010. Follow-up occurred with a maximum of 3 telephone calls 1 wk later to gauge interests and written informed consent was obtained from all participants. Previously, 87% of all eligible patients were enrolled using this recruitment method.[13]

This study included lung cancer survivors with pathologic and presumed lung cancer diagnoses (ie, those with lung nodules deemed by the chest tumor board to have high pre-test probability for lung cancer but at high risk for severe complications from tissue biopsy) who completed lung cancer resection surgery, definitive radiation, or concurrent chemoradiation for stage I-IIIA disease ≥1 mo previously. The study excluded patients who had progressive/recurrent lung cancer or were unable to follow directions and/or physically perform functional EC evaluation: severe dementia, bilateral below-knee amputation, or quadriplegia, and active systemic treatment for other cancers. A thorough list of clinical variables related to lung cancer and/or cardiopulmonary health were collected using data from the electronic health records. These included age, sex, body mass index, tobacco exposure, comorbidities (including COPD, heart failure with reduced ejection fraction [HFrEF], psychiatric illness), lung function (forced expiratory volume in the first second of expiration [FEV_1], diffusion of the lung for carbon monoxide, total lung capacity), and echocardiographic findings where available. Chronic obstructive pulmonary disease was defined as clinical documentation of COPD by a pulmonologist and/or postbronchodilator FEV_1/forced vital capacity <0.7 on spirometry, HFrEF as clinical documentation of systolic heart failure or echocardiographic ejection fraction ≤50%, and psychiatric illness as anxiety, depression, or post-traumatic stress disorder documented by a psychiatrist and/or active prescriptions of anxiolytics or antidepressants. Lung cancer characteristics included clinical stage and treatment modality. Time since treatment completion was also included to assess the possible effects of treatment or recovery on outcomes. All data were collected by a board-certified physician with subspecialty training in pulmonology (D.H.).

DYSPNEA ASSESSMENTS

Dyspnea was assessed using the LC13[14] and the University of California San Diego Shortness of Breath Questionnaire (SOBQ).[16] The LC13-Dyspnea score was used for primary analyses due to previous validation in the lung cancer population.[14] The LC13 is a 13-item questionnaire designed to assess lung cancer–associated symptoms (cough, dyspnea, hemoptysis, and pain) and chemo- and radiotherapy side effects (dysphagia, hair loss, neuropathy, sore mouth); dyspnea is assessed by 3 items on perceived shortness of breath at rest, when walking, and climbing stairs, scored as a mean of the component items with raw score range of 0 to 100.[14] Abnormally high dyspnea was defined as LC13-Dyspnea scores greater than mean reference value.[17] The SOBQ was used to replicate findings. The SOBQ is a 24-item questionnaire designed to assess self-reported shortness of breath with a variety of activities of daily living in patients with chronic lung disease[16] that has previously been used in lung cancer survivors[13,18]; responses are summed to a score range of 0 to 120.[16] In both the L13 and SOBQ questionnaires, higher scores indicate a higher level of perceived dyspnea. All questionnaire assessments were performed at the same time on printed forms without any modifications and prior to functional EC testing.

FUNCTIONAL EC

The primary outcome was functional EC as assessed by the 6-minute walk test, performed according to the standard protocol recommended by the American Thoracic Society Pulmonary Function Standards Committee.[19] In lung cancer survivors, the 6-min walk test distance (6MWD) has been validated against the gold standard of cardiopulmonary fitness (maximal EC, maximal or peak oxygen uptake) (concurrent validity),[20] shown to decrease with treatment (responsiveness),[21] shown to be low compared with general age-, sex-, height-, and weight-matched adults (discriminant validity),[13] and was independently associated with cancer-specific QoL (predictive validity).[13]

STATISTICAL ANALYSES

Descriptive statistics were summarized as appropriate; both L13-Dyspnea and SOBQ scores were analyzed as continuous variables. Univariable (UVA) and multivariable (MVA) linear regressions were used to analyze the relationship between all collected clinical characteristics and identify predictors or determinants of dyspnea and analyze the relationship between dyspnea and functional EC.

For MVAs, stepwise, backward selection modeling was used, starting with all variables with $P < .10$ in UVAs; those with the largest P values were sequentially eliminated from the models until all remaining variables were associated with the dependent variable (dyspnea or functional EC) at $P < .10$. Results were interpreted using regression coefficients (β), 95% CI, and coefficients of determination (R^2 and partial R^2), and statistical significance was defined as $P < .05$ in 2-tailed tests. All data were managed with REDCap electronic data capture tools[22] hosted at the local institution and analyzed as available without imputation using IBM SPSS Statistics software versions 25 and 26.

RESULTS

This study enrolled 75 lung cancer survivors at a median of 12 mo since completing curative-intent therapy. Their baseline clinical characteristics are described in Table 1. Most were white males with a history of tobacco use, concomitant COPD, and underwent either lung cancer resection surgery or definitive radioablation for the treatment of stage I non–small cell lung cancer (NSCLC).

DYSPNEA AND FUNCTIONAL EC

All participants completed dyspnea and 6MWD assessments. The LC13-Dyspnea and SOBQ scores were 35.3 ± 26.2 and 34.8 ± 25.6, respectively. These scores correlated very well ($r = 0.84$, $P < .001$) (see Supplemental Digital Content 2, available at: http://links.lww.com/JCRP/A133). Forty-five participants (60%) had abnormally high dyspnea, defined as LC13-Dyspnea raw score greater than mean reference value for patients with lung cancer (29.5).[17] The 6MWD was 347.9 ± 124.2 m (67% of predicted values in healthy adults[23]) (Table 1).

PREDICTORS OR DETERMINANTS OF DYSPNEA

Clinical variables borderline significantly ($P < .10$) associated with dyspnea are shown in Supplemental Digital Content 3, available at: http://links.lww.com/JCRP/A134. In MVAs (β [95% CI]), psychiatric illness (−20.8 [−32.4 to −9.09] for *No/Yes*), HFrEF (−15.5 [−28.0 to −2.97] for *No/Yes*), and FEV_1 (−0.28 [−0.49 to −0.06] for each % predicted) were significant independent predictors or determinants of dyspnea as determined from the LC13. Time since treatment completion was not associated with dyspnea. Results were similar with the SOBQ (Table 2; Figure 1A and B).

Table 1

Participant Characteristics

Participant Characteristic (N = 75, VASDHS, 2016-2018)	Value
Age, yr	70.7 ± 8.4
Male sex	71 (95)
Race	
Asian	4 (5)
Black	2 (3)
Hispanic	1 (1)
White	68 (91)
BMI, kg/m^2	26.8 ± 4.8
Smoking history	
Current	24 (32)
Former	44 (59)
Never	7 (9)
Pack yr	52.0 ± 31.7
Comorbidities	
Hypertension	61 (81)
Hyperlipidemia	60 (80)
Diabetes mellitus	21 (28)
Atrial fibrillation/flutter	18 (24)
CAD	26 (35)
COPD	56 (75)
HFrEF[a]	18 (24)
Diastolic dysfunction[b]	37 (79)
OSA	17 (23)
Anxiety/depression/PTSD	22 (29)
Other cancer	30 (40)
Pulmonary function[c]	
FEV_1/FVC, %	59.6 ± 14.6
FEV_1, % predicted	70.7 ± 25.0
TLC, % predicted[b]	110.8 ± 21.5
DL_{CO}, % predicted	78.5 ± 25.4
Lung function abnormality[d]	
Obstructive[d]	57 (76)
Hyperinflated[d]	18 (28)
DL_{CO} limited[d]	41 (55)
Lung cancer	
Clinical stage	
IA	50 (67)
IB	9 (12)
IIA	3 (4)
IIB	11 (15)
IIIA	2 (3)
Histology	
Adenocarcinoma	37 (49)
Squamous cell carcinoma	18 (24)
Presumed	15 (20)
Primary treatment	
Surgical resection	37 (49)
Definitive radioablation	27 (36)
Chemoradiation	11 (15)
Months since treatment	
Median	12.2
Interquartile range	1.8, 35.6
Dyspnea scores	
LC13-Dyspnea, point	35.3 ± 26.2
SOBQ, point	34.8 ± 25.6
Functional EC (6MWD), m	347.9 ± 124.2

(*continues*)

Table 1

Participant Characteristics (*Continued*)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; EC, exercise capacity; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HFrEF, heart failure with reduced ejection fraction; LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13; OSA, obstructive sleep apnea; PTSD, post-traumatic stress disorder; 6MWD, 6-minute walk distance; SOBQ, University of California San Diego Shortness of Breath Questionnaire; TLC, total lung capacity; VASDHS, VA San Diego Healthcare System. Data reported as mean ± SD or n (%).

[a]Defined as ejection fraction ≤50% or clinical documentation of systolic heart failure.

[b]Data available in 64 participants (85%) for TLC % predicted and 47 (63%) for diastolic dysfunction.

[c]Data obtained after completion of lung cancer treatment in 32 (43%) participants.

[d]Defined as FEV_1/FVC <70% for obstructive defect, TLC % predicted >120 for hyperinflation, and DL_{CO} % predicted <80 for DL_{CO} limitation.

Dyspnea Is an Independent Predictor of Functional EC

Results of UVAs to identify predictors of functional EC are shown in Table 3. In MVAs starting with all baseline clinical characteristics borderline significantly associated with functional EC, dyspnea was found to be an independent predictor of functional EC (−1.54 [−2.43 to −0.64] for each point) (Table 4; Figure 2A). These results were replicated by the SOBQ (−1.70 [−2.62 to −0.78]) (Table 4; Figure 2B).

DISCUSSION

In an analysis of data from a cross-sectional study of veteran lung cancer survivors following curative-intent therapy, this study found abnormally high dyspnea in most patients and identified 3 important clinical predictors or determinants of dyspnea: psychiatric illness (anxiety/depression/post-traumatic stress disorder), HFrEF, and physiological measure of obstructive ventilatory defect (FEV_1). In addition, dyspnea was an independent predictor of functional EC and accounted for 14-16% of its variance. These results highlight the importance of dyspnea in early-stage lung cancer survivorship and have implications for interventions aimed at improving exercise, function, and QoL in these patients.

The Institute of Medicine emphasizes the fundamental importance of care in the post-treatment phase of cancer survivorship, including supportive services to promote health and reduce long-term and late treatment effects.[24] Exercise is recommended by the American College of Sports Medicine[2] and the American Cancer Society[3] for many cancer survivors to promote health and reduce functional and QoL impairments. These recommendations are based on evidence of effectiveness in breast, prostate, and colon cancer survivors[25-27]; however, this evidence is not as consistent in lung cancer survivors.[4] Recent systematic reviews of exercise interventions in lung cancer survivors suggest that while exercise training as part of rehabilitation programs can improve functional EC and QoL following curative-intent therapy,[28-31] concerns for selection bias and inadequate sample size exist.[28,29,32] Moreover, a recent systematic review identified numerous patient-related barriers to regular exercise in lung cancer survivors.[33] These include physical capacity, symptoms, comorbidities, previous sedentary lifestyle, and psychological influences.[33]

Lung cancer survivors are different from other cancer populations due to a higher median age at diagnosis, lifetime exposure to tobacco, and prevalence of pulmonary and

Table 2

MVA—Independent Predictors or Determinants of Dyspnea

Variable	Unstandardized β (95% CI)	Standardized β	Partial R^2	*P* Value
LC13-Dyspnea[a]				
HFrEF (N/Y)	−15.5 (−28.0 to −2.97)	−0.25	0.08	.02
Anxiety/depression/PTSD (N/Y)	−20.8 (−32.4 to −9.09)	−0.36	0.15	.001
FEV_1 % predicted	−0.28 (−0.49 to −0.06)	−0.27	0.09	.01
SOBQ[b]				
HFrEF (N/Y)	−15.8 (−27.9 to −3.63)	−0.27	0.10	.01
Anxiety/depression/PTSD (N/Y)	−17.0 (−29.0 to −4.91)	−0.31	0.12	.01
Lung hyperinflation[c] (N/Y)	−11.0 (−23.3 to 1.21)	−0.20	0.05	.08
FEV_1 % predicted	−0.34 (−0.56 to −0.11)	−0.33	0.13	.004

Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; HFrEF, heart failure with reduced ejection fraction; LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13; PTSD, post-traumatic stress disorder; SOBQ, University of California San Diego Shortness of Breath Questionnaire.

[a]Overall model $R^2 = 0.26$, $P < .001$; no significant interaction between HFrEF and anxiety/depression/PTSD ($P = .14$) or anxiety/depression/PTSD and FEV_1 % predicted ($P = .48$).

[b]Overall model $R^2 = 0.37$, $P < .001$; no significant interaction between HFrEF and anxiety/depression/PTSD ($P = .15$), or anxiety/depression/PTSD and FEV_1 % predicted ($P = .68$).

[c]Data available in 64 participants.

cardiovascular comorbidities.[5] The median age at lung cancer diagnosis is 70 yr.[34] Most of lung cancer cases are caused by cigarette smoking,[35] which has many adverse health consequences. The most common comorbidities in patients with lung cancer, all of which can progressively and negatively impact health, are COPD,[36,37] diabetes, and heart failure, prevalent in 50-70%, 16%, and 13% of patients, respectively.[5] In addition, the effects of curative-intent therapy of lung cancer have unique effects on cardiopulmonary health since part of the therapy requires local destruction and/or removal of lung tissue, which may exacerbate symptoms and impede function and EC in some patients, making typical exercise interventions inaccessible.[31] The characterization of dyspnea may provide important insights into strategies to effectively improve exercise in this group of cancer survivors.

The mechanisms of dyspnea are incompletely understood[38]; however, peripheral sensors including through reflex chemoreceptor stimulation by carbon dioxide, pulmonary vagal C-fibers, mechanoreceptors, and central pathways (specifically the limbic system and sensorimotor

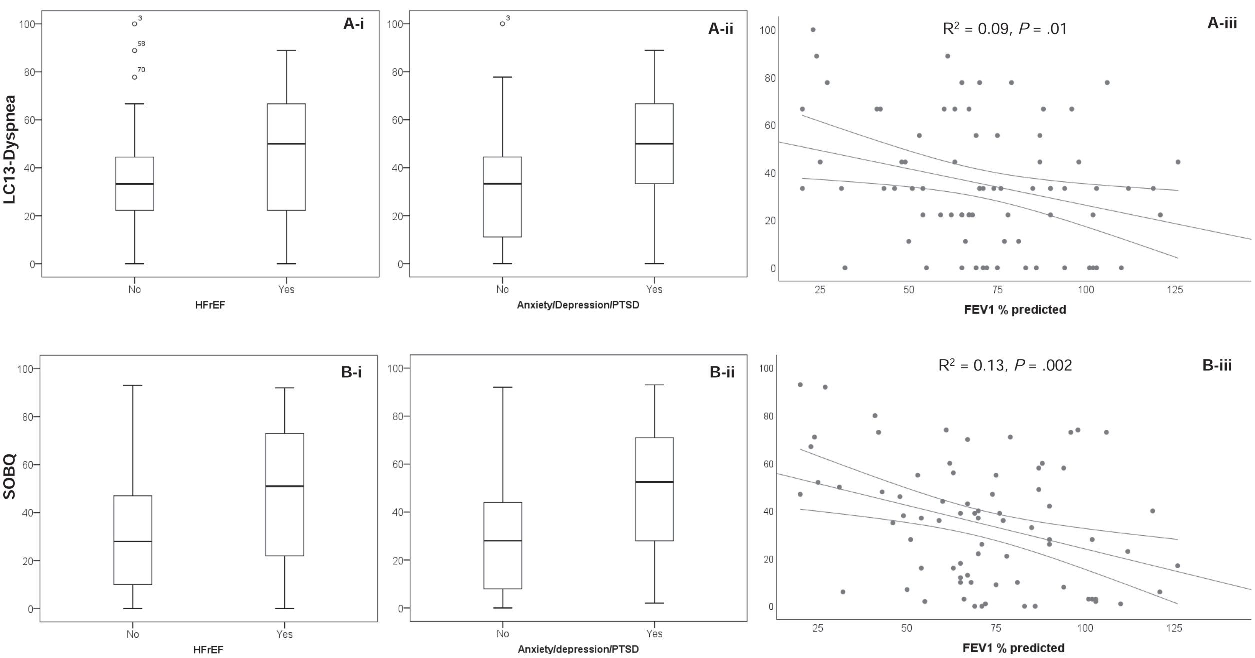

Figure 1. Clinical predictors or determinants of dyspnea. (A) Dyspnea scores as assessed by the LC13 by (i) HFrEF; mean ± SE difference = 15.3 ± 6.91, *P* = .03. (Independent-samples *t* tests, equal variances assumed.) (ii) Anxiety/depression/PTSD; mean ± SE difference = 19.4 ± 6.30, *P* = .003. (Independent-samples *t* tests, equal variances assumed.) (iii) FEV_1 % predicted; R^2 values derived from univariable linear regression analyses (UVAs) as listed in Supplemental Digital Content 3, available at: http://links.lww.com/JCRP/A134. (B) Dyspnea scores as assessed by the SOBQ by (i) HFrEF; mean ± SE difference = 16.5 ± 6.69, *P* = .02. (Independent-samples *t* tests, equal variances assumed.) (ii) Anxiety/depression/PTSD; mean ± SE difference = 19.9 ± 6.10, *P* = .002. (Independent-samples *t* tests, equal variances assumed.) (iii) FEV_1 % predicted; R^2 values derived from UVAs as listed in Supplemental Digital Content 3, available at: http://links.lww.com/JCRP/A134. Abbreviations: FEV_1, forced expiratory volume in the first second of expiration; HFrEF, heart failure with reduced ejection fraction; LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13; PTSD, post-traumatic stress disorder; SOBQ, University of California San Diego Shortness of Breath Questionnaire.

Table 3

Univariable Linear Regression Analysis—Significant/Borderline Predictors of Functional Exercise Capacity

Variable	Unstandardized β	Standardized β	R^2	*P* Value
Age, yr	−4.58	−0.31	0.10	.01
Hyperlipidemia (N/Y)	86.2	0.28	0.08	.02
CAD (N/Y)	68.5	0.26	0.07	.02
FEV_1 % predicted	0.96	0.19	0.04	.097
DL_{CO} % predicted	2.07	0.42	0.18	<.001
Adenocarcinoma histology (N/Y)	−82.0	−0.33	0.11	.004
Primary treatment group	N/A	N/A	0.18	.001
Dyspnea scores, each point				
LC13	−1.49	−0.31	0.10	.01
SOBQ	−1.85	−0.38	0.15	.001

Abbreviations: β, regression coefficient; CAD, coronary artery disease; DL_{CO}, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in the first second of expiration; LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13; SOBQ, University of California San Diego Shortness of Breath Questionnaire.

cortex) are thought to play important roles.[38] In lung cancer survivors following curative-intent therapy, dyspnea can be made worse due to a loss of 10-15% of lung function from lobectomy.[39] In addition, other possible pathophysiological effects may include a loss of associated nerve fibers and peripheral sensors due to the removal and/or destruction of lung tissue by surgery and/or radiotherapy. Adjuvant chemotherapy has been shown to cause peripheral neuropathy[40] and, therefore, possibly also vagal perturbations. These effects may accumulatively result in neuromechanical dissociation, which is implicated in the pathogenesis of dyspnea.[41]

Importantly, dyspnea was independently associated with functional EC in this study. For each 1-point increase in baseline dyspnea score, there was a 1.5- to 1.7-m decrease in the 6MWD. The association between dyspnea and functional EC has been described in other patient populations including COPD.[42] To the best of our knowledge, this relationship has not been previously characterized in lung cancer survivors following curative-intent therapy, many of whom experience worsening of dyspnea[6] as laid out previously. Moreover, a previous analysis of 359 postsurgical, stage I NSCLC survivors showed that dyspnea was significantly associated with physical health.[10] In fact, of all the variables included in that study,[10] dyspnea had approximately twice the effect size (β) on physical health as the next 2 largest effect sizes (employment status and depression symptoms). Another study also confirmed this large effect size of dyspnea on physical health.[43] These findings suggest that alleviating dyspnea may be a key factor to improve exercise in these patients.

The prevalence of abnormally high dyspnea in the current study (60%) is similar to previous reports in lung cancer survivors following curative-intent therapy.[8-11] In 1 study,[8] the prevalence of COPD (23%) was significantly lower (75%), while the prevalence of abnormal/clinically significant dyspnea was the same. In that study, 65% dyspneic patients reported not having dyspnea preoperatively, suggesting treatment-related effects.[8] Moreover, LC13 dyspnea scores were reported to be higher in 830 post-surgical lung cancer survivors than in propensity-matched individuals from the general population, particularly in those with cardiac or pulmonary comorbidity and in those treated with combined modality therapy.[44] Results in the current study showed an association between treatment type and dyspnea scores only in univariable (see Supplemental Digital Content 3, available at: http://links.lww.com/JCRP/A134) but not in multivariable (Table 2) analyses, possibly

Table 4

Dyspnea Is an Independent Predictor of Functional Exercise Capacity

Variable	Unstandardized β (95% CI)	Standardized β	Partial R^2	*P* Value
Model 1[a,b] (LC13-Dyspnea)				
Age, yr	−5.81 (−8.54 to −3.08)	−0.39	0.21	<.001
Hyperlipidemia (N/Y)	72.0 (15.9-128.0)	0.23	0.09	.01
DL_{CO} % predicted	1.81 (0.90-2.73)	0.37	0.18	<.001
LC13-Dyspnea, point	−1.54 (−2.43 to −0.64)	−0.32	0.14	.001
Model 2[b,c] (SOBQ)				
Age, yr	−5.86 (−8.55 to −3.16)	−0.40	0.21	<.001
Hyperlipidemia (N/Y)	61.6 (6.62-116.6)	0.20	0.07	.03
DL_{CO} % predicted	1.70 (0.79-2.62)	0.35	0.16	<.001
SOBQ, point	−1.70 (−2.62 to −0.78)	−0.35	0.16	<.001

Abbreviations: DL_{CO}, diffusion capacity of the lung for carbon monoxide; LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13; SOBQ, University of California San Diego Shortness of Breath Questionnaire.

[a]Overall model $R^2 = 0.45$, $P < .001$; no significant interaction between age and LC13-Dyspnea ($P = .40$), or DL_{CO} % predicted and LC13-Dyspnea ($P = .30$).

[b]Covariates selected to enter model ($P < .1$): age, hyperlipidemia, coronary artery disease, forced expiratory volume in the first second of expiration (FEV_1) % predicted, DL_{CO} % predicted, adenocarcinoma, and treatment group (Table 3).

[c]Overall model $R^2 = 0.46$, $P < .001$; no significant interaction between age and SOBQ ($P = .995$), or DL_{CO} % predicted and SOBQ ($P = .55$).

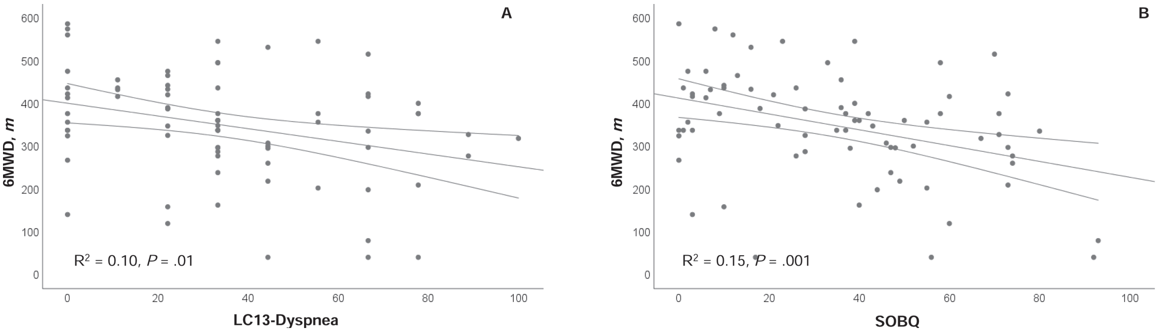

Figure 2. Dyspnea is an independent predictor of functional exercise capacity (6MWD). (A) Dyspnea as assessed by the LC13. (B) Dyspnea as assessed by the SOBQ, R^2 values derived from univariable linear regression analyses as listed in Table 3. LC13, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module 13; 6MWD, 6-minute walk distance; SOBQ, University of California San Diego Shortness of Breath Questionnaire.

due to a small sample size and/or inclusion of lung function. The predictors or determinants of dyspnea identified offer complimentary information to a previous report in 342 post-surgical NSCLC survivors[8] and another in 142 long-term, post-surgical NSCLC survivors.[43] In addition, HFrEF and psychiatric illness were identified as predictors or determinants, which have clinical management implications in these patients.

This study has novel insights. Historically, most lung cancer cases were diagnosed at advanced stages and treated with palliation. However, the landscape for lung cancer is changing rapidly[45] due to advances in screening,[46,47] diagnostic,[48] and therapeutic[49,50] modalities. As the number of earlier-stage lung cancer survivors increases,[51,52] more attention must be paid to the unique health challenges faced by this group of cancer survivors.[12] A prospective study was recently completed which showed that dyspnea symptoms worsen at 1 to 3 mo following curative-intent lung cancer treatment.[53] As such, it is postulated that in order to maximize efforts to improve exercise, function, and QoL in lung cancer survivors following curative-intent treatment, optimizing medical therapy for cardiopulmonary disease[54] and possibly psychiatric illness[55] to alleviate dyspnea may also be important. Recent randomized controlled trials in patients with COPD have shown that combination long-acting muscarinic-antagonist and β-agonist inhaler therapy is effective in reducing dyspnea[56] and, possibly, in improving physical activity.[57,58] Initiation of combination long-acting muscarinic-antagonist and β-agonist bronchodilators, particularly in survivors with concomitant COPD, may be an important first step. Moreover, while exercise training as part of comprehensive rehabilitation programs may improve function and QoL in lung cancer survivors, studies in patients with chronic lung disease show that the benefits of exercise training wane over time, as patients do not increase or maintain activity outside the training setting.[59] A recent systematic review of exercise programs in lung cancer survivors identified the need for home-based exercise programs,[31] reported by many cancer survivors to be more desirable.[60] In addition, traditional exercise interventions focus on moderate to vigorous intensity exercise. More recently, light-intensity exercise and sedentary behavior are also recognized as important in health promotion: the US Department of Health & Human Services emphasized that moving more and sitting less will benefit nearly everyone.[61] Therefore, in addition to reducing dyspnea, exercise interventions in lung cancer survivors may need to also promote light-intensity exercise and reduce sedentary behavior to be effective (see Supplemental Digital Content 1, available at: http://links.lww.com/JCRP/A132).

This study has limitations. First, despite a thorough list of important clinical characteristics in the lung cancer population, only 30-40% of the variances in dyspnea scores were explained. However, to the best of our knowledge, no other studies have reported higher R^2 values including those reported in a large, international, population-based study involving 9484 participants with many demographic and clinical variables (largest R^2 reported = 0.13).[62] Second, the cross-sectional and descriptive nature of this study provides no insight on the effects of lung cancer treatment on dyspnea, the underlying physiobiological mechanism, or how to effectively alleviate it; information on medical therapy for comorbidities was not collected, limiting the ability to draw conclusions between medical therapy and dyspnea scores. Third, these findings may have limited generalizability due to it being a single-institutional study involving a predominantly white male veteran patient population with significant tobacco exposure and higher prevalence of COPD and psychiatric illness.[5] Fourth, lung function (FEV_1) but not a spirometric diagnosis of COPD was associated with dyspnea in this study, which may be due to the small sample size and/or a limitation in data containing both pre- and post-treatment lung function. Fifth, in this study, 35% of lung cancer survivors had coronary artery disease, 40% had previous history of other cancers, and 79% of those who had undergone echocardiography had diastolic dysfunction, all of which could additionally impact dyspnea. These variables were not significantly associated with dyspnea, possibly due to a small sample size.

The strengths of this study include a detailed list of comorbidities and physiological measures of cardiopulmonary health including lung function, all of which were entered in the electronic medical record and collected by board-certified physicians, maximizing the accuracy of the data obtained. In addition, all patient reported outcome and functional EC assessments were performed in-person by 1 observer (D.H.), maximizing the completeness and accuracy of the data collected and minimizing interobserver variability. Finally, the findings were verified using a second dyspnea questionnaire, maximizing the validity of the conclusions.

In conclusion, abnormally high dyspnea was prevalent in ≥50% of lung cancer survivors following curative-intent therapy, partly due to underlying psychiatric illness, presence of HFrEF, and obstructive ventilatory defects. In addition, dyspnea was a significant independent predictor of functional EC. Efforts to improve exercise, function, and QoL in lung cancer survivors may need to also focus on optimizing therapy for comorbid cardiopulmonary and/or psychiatric illnesses and reduce dyspnea to be effective.

REFERENCES

1. Buffart LM, Kalter J, Sweegers MG, et al. Effects and moderators of exercise on quality of life and physical function in patients with cancer: an individual patient data meta-analysis of 34 RCTs. *Cancer Treat Rev*. 2017;52:91-104.
2. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42:1409-1426.
3. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62:243-274.
4. Bade BC, Thomas DD, Scott JB, Silvestri GA. Increasing physical activity and exercise in lung cancer: reviewing safety, benefits, and application. *J Thorac Oncol*. 2015;10:861-871.
5. Islam KM, Jiang X, Anggondowati T, Lin G, Ganti AK. Comorbidity and survival in lung cancer patients. *Cancer Epidemiol Biomarkers Prev*. 2015;24:1079-1085.
6. Sarna L, Cooley ME, Brown JK, Chernecky C, Elashoff D, Kotlerman J. Symptom severity 1 to 4 months after thoracotomy for lung cancer. *Am J Crit Care*. 2008;17:455-467.
7. Win T, Groves AM, Ritchie AJ, Wells FC, Cafferty F, Laroche CM. The effect of lung resection on pulmonary function and exercise capacity in lung cancer patients. *Respir Care*. 2007;52:720-726.
8. Feinstein MB, Krebs P, Coups EJ, et al. Current dyspnea among long-term survivors of early-stage non-small cell lung cancer. *J Thorac Oncol*. 2010;5:1221-1226.
9. Lowery AE, Krebs P, Coups EJ, et al. Impact of symptom burden in post-surgical non-small cell lung cancer survivors. *Support Care Cancer*. 2014;22:173-180.
10. Ostroff JS, Krebs P, Coups EJ, et al. Health-related quality of life among early-stage, non-small cell, lung cancer survivors. *Lung Cancer*. 2011;71:103-108.
11. Yang P, Cheville AL, Wampfler JA, et al. Quality of life and symptom burden among long-term lung cancer survivors. *J Thorac Oncol*. 2012;7:64-70.
12. Vijayvergia N, Shah PC, Denlinger CS. Survivorship in non-small cell lung cancer: challenges faced and steps forward. *J Natl Compr Canc Netw*. 2015;13:1151-1161.
13. Ha D, Ries AL, Mazzone PJ, Lippman SM, Fuster MM. Exercise capacity and cancer-specific quality of life following curative intent treatment of stage I-IIIA lung cancer. *Support Care Cancer*. 2018;26:2459-2469.
14. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer*. 1994;30A:635-642.
15. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573-577.
16. Eakin EG, Resnikoff PM, Prewitt LM, Ries AL, Kaplan RM. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. *Chest*. 1998;113:619-624.
17. Scott NW, Fayers PM, Aaronson NK, et al. EORTC QLQ-C30 reference values. *EORTC Qual Life Group* [serial online]. http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf. Published 2008. Accessed January 2017.
18. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. The impact of adjuvant brachytherapy with sublobar resection on pulmonary function and dyspnea in high-risk patients with operable disease: preliminary results from the American College of Surgeons Oncology Group Z4032 trial. *J Thorac Cardiovasc Surg*. 2011;142:554-562.
19. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111-117.
20. Schmidt K, Vogt L, Thiel C, Jager E, Banzer W. Validity of the six-minute walk test in cancer patients. *Int J Sports Med*. 2013;34:631-636.
21. Granger CL, Holland AE, Gordon IR, Denehy L. Minimal important difference of the 6-minute walk distance in lung cancer. *Chron Respir Dis*. 2015;12:146-154.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377-381.
23. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158:1384-1387.
24. Institute of Medicine, committee on quality of healthcare in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: The National Academies Press; 2001.
25. Skolarus TA, Wolf AM, Erb NL, et al. American Cancer Society prostate cancer survivorship care guidelines. *CA Cancer J Clin*. 2014;64:225-249.
26. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. *CA Cancer J Clin*. 2016;66:43-73.
27. El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society colorectal cancer survivorship care guidelines. *CA Cancer J Clin*. 2015;65:428-455.
28. Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. *Cochrane Database Syst Rev*. 2013;(7):CD009955.
29. Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training for people following lung resection for non-small cell lung cancer—a Cochrane systematic review. *Cancer Treat Rev*. 2014;40:585-594.
30. Ni HJ, Pudasaini B, Yuan XT, Li HF, Shi L, Yuan P. Exercise training for patients pre- and postsurgically treated for non-small cell lung cancer: a systematic review and meta-analysis. *Integr Cancer Ther*. 2017;16:63-73.
31. Driessen EJ, Peeters ME, Bongers BC, et al. Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: a systematic review. *Crit Rev Oncol Hematol*. 2017;114:63-76.
32. Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev*. 2017;6:CD012020.
33. Granger CL, Connolly B, Denehy L, et al. Understanding factors influencing physical activity and exercise in lung cancer: a systematic review. *Support Care Cancer*. 2017;25:983-999.
34. National Cancer Institute—Surveillance, Epidemiology, and End Results Program. Lung and bronchus cancer. https://seer.cancer.gov/statfacts/. Accessed March 3, 2018.
35. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e1S-e29S.
36. Ytterstad E, Moe PC, Hjalmarsen A. COPD in primary lung cancer patients: prevalence and mortality. *Int J Chron Obstruct Pulmon Dis*. 2016;11:625-636.
37. Spyratos D, Papadaki E, Lampaki S, Kontakiotis T. Chronic obstructive pulmonary disease in patients with lung cancer: prevalence, impact and management challenges. *Lung Cancer (Auckl)*. 2017;8:101-107.
38. Burki NK, Lee LY. Mechanisms of dyspnea. *Chest*. 2010;138:1196-1201.
39. Kim HK, Lee YJ, Han KN, Choi YH. Pulmonary function changes over 1 year after lobectomy in lung cancer. *Respir Care*. 2016;61:376-382.
40. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med*. 2005;352:2589-2597.
41. O'Donnell DE. Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2006;3:180-184.
42. Spruit MA, Watkins ML, Edwards LD, et al. Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort. *Respir Med*. 2010;104:849-857.
43. Sarna L, Evangelista L, Tashkin D, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. *Chest*. 2004;125:439-445.
44. Yun YH, Kim YA, Min YH, et al. Health-related quality of life in disease-free survivors of surgically treated lung cancer compared with the general population. *Ann Surg*. 2012;255:1000-1007.

45. Vachani A, Sequist LV, Spira A. AJRCCM: 100-year anniversary. The shifting landscape for lung cancer: past, present, and future. *Am J Respir Crit Care Med*. 2017;195:1150-1160.
46. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395-409.
47. Mazzone PJ, Silvestri GA, Patel S, et al. Screening for lung cancer: CHEST guideline and expert panel report. *Chest*. 2018;153:954-985.
48. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e142S-e165S.
49. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143:e278S-e313S.
50. Donington J, Ferguson M, Mazzone P, et al. American college of chest physicians and society of thoracic surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest*. 2012;142:1620-1635.
51. Lou Y, Dholaria B, Soyano A, et al. Survival trends among non-small-cell lung cancer patients over a decade: impact of initial therapy at academic centers. *Cancer Med*. 2018;7:4932-4942.
52. Boyer MJ, Williams CD, Harpole DH, Onaitis MW, Kelley MJ, Salama JK. Improved survival of stage I non-small cell lung cancer: a VA central cancer registry analysis. *J Thorac Oncol*. 2017;12:1814-1823.
53. Ha D, Ries AL, Lippman S, Fuster MM. Effects of curative-intent lung cancer therapy on functional exercise capacity and patient-reported outcomes. *BioRxiv (preprint)*. 2019; 508440. doi: doi:10.1101/508440.
54. Parshall MB, Schwartzstein RM, Adams L, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. *Am J Respir Crit Care Med*. 2012;185:435-452.
55. Barbetta C, Currow DC, Johnson MJ. Non-opioid medications for the relief of chronic breathlessness: current evidence. *Expert Rev Respir Med*. 2017;11:333-341.
56. Ni H, Moe S, Soe Z, Myint KT, Viswanathan KN. Combined aclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2018;12:CD011594.
57. Ichinose M, Minakata Y, Motegi T, et al. Efficacy of tiotropium/olodaterol on lung volume, exercise capacity, and physical activity. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1407-1419.
58. Watz H, Troosters T, Beeh KM, et al. ACTIVATE: the effect of aclidinium/formoterol on hyperinflation, exercise capacity, and physical activity in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2545-2558.
59. Spruit MA, Pitta F, McAuley E, ZuWallack RL, Nici L. Pulmonary rehabilitation and physical activity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192:924-933.
60. Wong JN, McAuley E, Trinh L. Physical activity programming and counseling preferences among cancer survivors: a systematic review. *Int J Behav Nutr Phys Act*. 2018;15:48. doi:10.1186/s12966-018-0680-6.
61. US Department of Health & Human Services. Physical activity guidelines. https://health.gov/paguidelines/default.aspx. Published 2018. Updated May 22, 2019. Accessed May 22, 2019.
62. Gronseth R, Vollmer WM, Hardie JA, et al. Predictors of dyspnoea prevalence: results from the BOLD study. *Eur Respir J*. 2014;43:1610-1620.